MEDICAL STAFF CONFERENCE

Von Willebrand's Disease

Distinction from Other Syndromes Associated with a Long Bleeding Time, and from Hemophilia

DR. NAGEL:* The patient is a 43-year-old Mexican-American man who was admitted to the Fort Miley Veterans Administration Hospital, San Francisco, on referral from the Veterans Administration Hospital at Fresno for evaluation of hypercalcemia. The patient had had numerous episodes of minor epistaxis in early childhood, but the first major episode of bleeding occurred at the age of 15 following tonsillectomy. Subsequently bleeding difficulties followed a number of surgical procedures. He gave no history of intradermal hemorrhage, hemarthrosis, or gastrointestinal or genitourinary bleeding. One brother gave a similar history of bleeding. In the patient's past medical history the only item of note was bronchial asthma since age 18. Asthma became progressively worse in later life and because of it he had had to quit working six years ago. During a stay in hospital in April of 1968 for bronchial asthma, the patient was noted to have hypercalcemia which was unresponsive to low calcium diet and oral prednisone.

On physical examination at the time of admission to the University of California Medical Center, the patient's blood pressure was 138/90 mm of mercury, pulse rate 80, weight 242 pounds and height 6 feet 1 inch. He was in no apparent distress. Examination of the head, eyes, ears, nose, and throat revealed only a distorted nasal septum and a questionable tender mass over the left lower pole of the thyroid gland. On examination of the chest poor excursions, decreased breath sounds and scattered wheezes were noted. The heart sounds were diminished and the rhythm irregular. The abdomen was obese and without palpable organomegaly. No petechiae or areas of ecchymosis were evident.

Laboratory data from the Veterans Administration Hospital included a hematocrit of 39 percent, a white count of 4,900 per cu mm with platelets of 178,000 per cu mm. Duke bleeding time was 2 minutes (normal). Prothrombin time was 100 percent. Clotting time (Lee and White) was 12 minutes and 18 minutes on two separate occasions. Calcium was 12.2 mg and phosphorus 2.1 mg per 100 ml. Creatinine was 1.0 and a serum protein electrophoresis was described as being normal. The patient was referred for additional laboratory studies (Table 1). Platelet adhesiveness was 19 percent (low) and the partial thromboplastin time was 70.8 seconds with a control of 41.

The thromboplastin generation time is of interest in that the absorbed plasma of a normal person corrected this patient's deficiency. As you recall, absorbed plasma contains Factor V, VIII, XI, and XII. The specific assay for Factor VIII disclosed a level of 6 percent.

X-ray examination disclosed nothing of pathological significance.

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TABLE 1.—*Hemostatic Studies on Patient*

Bleeding time (Ivy)	2 minutes
Platelet count	280,000 per mm³
Platelet adhesiveness (Salzman)	19%
Prothrombin time (Quick)	77%
Partial thromboplastin time	70.8" (control: 41.0")
Thrombin time	11.4" (control: 11.7")
Whole clot lysis	none
Clot retraction	normal

Thromboplastin generation test:

Absorbed Plasma	*Serum*	*Minutes of Generation* 2	4	6
normal	normal	>60"	15.7"	10.9"
patient	patient	>60"	>60"	>60"
patient	normal	>60"	>60"	53.0"
normal	patient	>60"	33.7"	11.0"

Specific coagulation factor assays:

Factor II (prothrombin) . . plasma 106% serum 5%
Factor VIII (AHF) 6%

DR. FUDENBERG:* This patient will be discussed by Dr. Herbert Perkins, who has had a long sustained interest in hemophilia and von Willebrand's disease. We will ask him to tell us about the factors necessary for diagnosis and also what therapy to use.

DR. PERKINS:† I get invited every few years to discuss von Willebrand's disease at these rounds. These repeated invitations result, I am sure, because inadequacies of the diagnostic tests employed and differences of opinion about classification of this and related defects leave the audience somewhat confused as to the exact criteria for definite diagnosis. The patient just presented offers an excellent illustration of the kind of diagnostic dilemma which may occur and how it may be resolved. Let me begin by saying that I use the term "von Willebrand's disease" to describe a congenital bleeding diathesis occurring in both sexes with a dominant inheritance and characterized primarily by bleeding from mucous membranes with the laboratory hallmarks of a prolonged bleeding time, decreased adhesiveness of platelets to glass, and a somewhat reduced level of Factor VIII, the antihemophilic factor (AHF). Von Willebrand's disease is characterized, in addition, by two rather unexpected findings. Although the defect seems to involve formation of the platelet plug, correction of the abnormal bleeding time is accomplished with transfusion of plasma and not with platelets.[1] In addition, transfusion of a variety of plasma derivatives results in a progressive rise in the Factor VIII level of the recipient to levels far higher than can be accounted for by the amount of Factor VIII transfused.

The confusions about von Willebrand's disease and the differences of opinion about classification arise from multiple sources. First, these patients tend to have borderline abnormalties in hemostatic tests. Clinically their bleeding is more likely to be a minor nuisance than presenting as a serious emergency for management of hemostasis. The borderline results of tests explain why abnormal answers may be obtained on one occasion; normal ones on the next. Moreover, the tests employed are quantitatively rather poorly reproducible, and I shall have more to say on this subject later. Finally, the type of bleeding seen in von Willebrand's disease and its association with a prolonged bleeding time are found in a number of other conditions, both congenital and acquired. Some authorities use the term "von Willebrand's disease" to include a wider spectrum of congenital bleeding syndromes than I have defined, considering it a "waste basket" with a variety of mechanisms involved.

A further complication in our understanding of von Willebrand's disease results from the fact that the *in vivo* evidence already mentioned,[1] which indicates that we must be dealing with a deficiency of a factor contained in the plasma, is not yet corroborated by any good *in vitro* evidence. It is currently believed that the first step in formation of a platelet plug is a specific attraction of platelets to exposed collagen fibers. Adenosine diphosphate (ADP) is then released, resulting in platelet aggregation. This last step requires calcium and one or more plasma cofactors.[2] This scheme would corroborate our *in vivo* evidence if we could identify the factor we tranfuse into these patients to shorten their bleeding time with the plasma cofactor of ADP aggregation. Unfortunately, none of the *in vitro* evidence seems to point in this direction[2]; in fact, fibrinogen seems to be at least one of the necessary plasma cofactors. This is a confusing point for which we have no good answers at the moment.

I would like now to discuss the diagnostic tests we use and the problems they create. The bleeding time determination is too often done in routine laboratories with a variety of implements that make incisions of varying depth and width. Under these conditions results are almost totally meaningless. Close reproducibility is difficult to obtain even with acceptable, well-standardized tests. The method of Duke (favored by hospital laboratories because

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TABLE 2.—*Related Data on Five Members of a Family In Which Three Had History of Bleeding*

	Age	Bleeding History	Bleeding Time	Factor VIII	Platelet Adhesiveness
Propositus	54	yes	30′	29%	0%
Son	33	yes	30′	28%	0%
Son's wife	36	no	5.5′	85%	47%
Granddaughter	10	no	2.5′	65%	52%
Grandson	8	yes	6′	36%	0%

of speed and simplicity) is not as sensitive as the technique of Ivy in which standard incisions are made in the forearm after application of a blood pressure cuff inflated to maintain a pressure of 40 mm of mercury. Nilsson and coworkers[3] demonstrated that patients with von Willebrand's disease and a prolonged Ivy bleeding time will, in approximately half of the cases, have a normal result with the Duke test. The Duke bleeding time will thus detect only the more severe cases of von Willebrand's disease. Although this will result in identification of the patients most likely to have serious clinical problems with hemostasis, the lesser sensitivity compared with the Ivy test explains some of the discrepant conclusions in the published literature. With either method borderline bleeding times may be encountered, and such patients may demonstrate an abnormality one time and not the next.

Published reports[4,5] of studies of families with von Willebrand's disease often point out the inconsistency of results among different involved members of the same family. Genetic mechanisms such as variable penetrance are often invoked as an explanation, but I believe that at least some of these differences may be attributed to the variability of our test results. Table 2 shows the data in one of our family studies. The propositus and his son and grandson clearly appear to share the defect. All results are classical for von Willebrand's disease except for normal bleeding time in the grandson. One could interpret this as variable penetrance; but this test was done only once, and I am more inclined to attribute it to variability in the laboratory test.

The Factor VIII assay also leads to trouble. Early reports on von Willebrand's disease emphasized the distinctive value of this test because its degree of reproducibility is excellent. Unfortunately, the levels encountered in von Willebrand's disease are again frequently in the borderline range.[6] Normal levels of Factor VIII extend from 50 to 200 percent of the mean; in von Willebrand's disease they are often in the 30-50 percent range. This leads to erroneous conclusions for two reasons. First, levels of antihemophilic factor rise with stress, and they do this in von Willebrand's disease as they do in normals. Often the initial blood sample is taken at a time of acute stress when the Factor VIII level has climbed into the normal range. The true deficiency can be established only later when baseline conditions are achieved. A second source of difficulty with borderline results is that a single sample may be reported as having 40-45 percent Factor VIII in one laboratory and 50-55 percent in another because of the simple fact that the standard Factor VIII preparations used as a criterion of 100 percent activity are not identical in the different laboratories.

The platelet adhesiveness test of Salzman has added further diagnostic help, but again further confusion. The test is performed by determining the loss of platelets after passage through a standard glass bead column directly from the blood stream into a tube with EDTA anticoagulant. Normally 26 to 60 percent of platelets are trapped by the column. The percent adhesiveness result thus obtained is the difference between two platelet counts. A glance at the table on page 54 of George Cartwright's book *Diagnostic Laboratory Hematology*[7] will convince you that a test which depends on the difference between two platelet counts cannot be highly reproducible in a quantitative sense. We have never found it reproducible enough to use as a test for monitoring the effect of therapy. We have, however, found it effective to a significant degree in distinguishing patients with von Willebrand's disease from normal persons. Our unpublished studies on 50 normal subjects demonstrated that there were 15 percent who had platelet adhesiveness values on a single occasion below the 26 percent accepted as the lower limit of normal; however, 79 percent of patients with von Willebrand's disease had abnormally low results. The differences are significant enough so that this test (in combination with other tests) helps to distinguish von Willebrand's disease, but the extent to which results in normal persons and affected patients overlap explains some of the confusion in published reports. Incidentally, the degree of overlap just mentioned coincides very closely with that obtained by a number of laboratories in an international cooperative study, as reported by Salzman[8] at a recent meeting of the National Hemophilia Foundation.

Turning from the problems created by the in-

adequacies of our diagnostic tests, I would now like to discuss clinical entities which may be confused with von Willebrand's disease. First, I would like you always to keep in mind that these include two rather common acquired defects. I am talking, of course, of uremia in which a qualitative platelet defect is the major cause of the prolonged bleeding time and of the dysproteinemias (especially macroglobulinemia) in which coating of platelets by the abnormal protein explains the defect. A closely similar condition can also be produced by transfusion of excessive amounts of dextran. These acquired conditions are distinguishable from von Willebrand's disease with relative ease.

We are still left with a large group of illnesses, which by history appear to be congenital, which should be distinguished from von Willebrand's disease because specific therapy required may not be the same. First to be considered are the qualitative platelet defects. In these there is usually a normal number of platelets, but their function is impaired. Traditionally these states have been classified into two groups: thrombasthenia, characterized primarily by a defect in clot retraction, and thrombocytopathy, which entails a failure to make the platelet phospholipid (factor 3) available for coagulation. As more patients have been studied, the distinction between these two categories of qualitative platelet defects has tended to become blurred. In some patients both types of abnormalities are demonstrated.

A qualitative platelet defect may be suspected initially from the appearance of platelets on the blood smear. Large, bizarre platelets with no tendency to clump may be seen. A second simple clue may come from failure of the clot to retract. This is one reason why this test should be included in routine hemostatic studies of bleeding patients. The prothrombin consumption test is a good indicator of the availability of platelet factor 3. More commonly used coagulation tests, such as the partial thromboplastin time, do not indicate platelet defects; platelet substitute is always provided in the form of cephalin. Other techniques which have been used to test the availability of platelet phospholipid for coagulation include the thromboplastin generation test (employing washed platelets of the patient) and incubation of platelet-rich plasma with kaolin. We find prothrombin consumption the simplest approach. We confirm the role of platelets in any defect demonstrated by showing that prothrombin consumption is normalized with added platelet substitute, following the suggestion of the Mayo Clinic group.[9]

The simple tests thus far discussed do not begin to take advantage of the sophisticated knowledge of platelet function which is exciting much attention nowadays. There are ways of testing the various phases of the mechanism of formation of the platelet plug, to which I have already referred. One can test for platelet affinity to collagen, for platelet responsiveness to ADP and other substances. Dr. Paul Aggeler's laboratory has experience with a battery of such tests.[10] With their aid, cases which superficially look very much like von Willebrand's disease may be established as having a qualitative platelet defect. So far as we know at the moment, however, these qualitative platelet defects make up a very small proportion of the long bleeding time syndromes I am discussing. The major definable group has von Willebrand's disease. There remain, however, a sizable proportion of patients with long bleeding times, normal Factor VIII levels, and (as yet) no defined qualitative platelet defect. Others with similar histories manifest various combinations of normal and abnormal results in the bleeding time, AHF assay, and platelet adhesiveness test. If bleeding is a serious problem in such a case, it may become necessary to determine by trial and error whether plasma (or its cryoprecipitate derivative) or platelets will correct the abnormal bleeding time. I should emphasize, however, that most of these patients do not have serious enough problems to justify transfusions even when surgical operation is contemplated.

Enough has been said to make it clear that it may at times be difficult to distinguish between von Willebrand's disease and mild hemophilia. The case under discussion today represents an example of this difficulty. The family history occasionally helps if the pattern of inheritance is clear. Our patient today had only one relative with a history of bleeding (his brother). This could be consistent with either disease. Bleeding was primarily from mucous membranes, with many nosebleeds as a child. There was no serious problem until age 15 when he bled abnormally after tonsillectomy. A later spinal operation was not associated with excessive blood loss. The platelet adhesiveness was 19 percent. All of these facts suggested that von Willebrand's disease is most likely. On the other hand bleeding time was normal, and the only involved relative was also a male. Hemophilia thus remained a definite possibility.

The diagnosis in this instance was of far greater importance than satisfying academic curiosity. The patient, already a serious operative risk, needs parathyroidectomy, and defective hemostasis in this area of the neck following operation could not be tolerated. We believed the importance of accurate diagnosis justified transfusion of an AHF concentrate to permit a conclusive diagnosis. Such trials are not loosely recommended because of the risk of inducing hepatitis.

The distinction between hemophilia and von Willebrand's disease can usually be established because the patient with hemophilia has a rise in AHF level to the point expected based on the amount of Factor VIII transfused and the plasma volume of the patient in which it is diluted. Peak values occur immediately, followed by curvilinear decay with a half-life of about ten hours. In contrast, the patient with von Willebrand's disease may, shortly after transfusion, have a Factor VIII level somewhat higher than expected, followed by a progressive *rise* for 24 to 48 hours.

Our patient was given 8 units of cryoprecipitate. His Factor VIII jumped to an immediate peak of 18 percent (almost identical with the predicted 17 percent) and then fell. Subsequent values plotted on semilogarithmic paper fell in a straight line with a half-life of 16 to 18 hours. The first gain from this test, then, was proof that he had classical hemophilia. Second, the rate of decay (somewhat slower than average) clearly proved he had no circulating anti-coagulant which might destroy transfused AHF. Third, we could now predict with considerable confidence how much Factor VIII it would take to raise this patient's level to any concentration we desired. We knew how much Factor VIII activity we had administered, and we knew how high that raised his level.

The fourth bit of information was unexpected: a very severe case of hives developed. Since we have had previous experiences in which severe allergic reactions resulting from transfusions were due to an antibody in the patient's serum reacting with a foreign type of IgA immunoglobulin in the donor plasma,[11] we had Dr. Vyas* test the patient's serum. Anti-IgA was found. We could not plan operation for this patient knowing that he might have an allergic reaction to the Factor VIII concentrate we were using, which might force us to interrupt therapy.

*Girish N. Vyas, Ph.D., Lecturer, Departments of Bacteriology, Immunology, and Medicine.

I have emphasized the importance of an exact diagnosis when control of bleeding by transfusion is required to permit operation, because it may dictate our choice of product for transfusion. The Factor VIII level of a patient with von Willebrand's disease is relatively easy to raise and can be maintained with relatively infrequent transfusions. It may be necessary, however, to correct the bleeding time also. I have mentioned that this may be accomplished by transfusion of plasma, but very large volumes are required.

Fortunately, cryoprecipitate (the Factor VIII concentrate which may be prepared in the blood bank) is an effective concentrate of the factor which corrects the bleeding time. Many of you remember a patient with von Willebrand's disease in this hospital who bled repeatedly and massively from the gastrointestinal tract.[1] His bleeding time was longer than 30 minutes, but his antihemophilic factor was usually in a range which should not have resulted in impaired hemostasis (40 to 45 percent). Three attempts to control gastrointestinal bleeding surgically resulted only in an increased rate of hemorrhage. The patient's bleeding time could be shortened by cryoprecipitate, but it required at least eight units in this 70 kg man, and even then the degree of shortening was often not into the normal range. It was enough, however, to achieve temporary control of hemostasis. Thus, cryoprecipitate is the recommended form of transfusion therapy for patients with von Willebrand's disease. Commercial Factor VIII concentrates so far tested do not contain the highly labile factor which corrects the bleeding time. This is obviously one important reason why we must distinguish between von Willebrand's disease and hemophilia. If hemophilia is present, commercial concentrates may be used (Table 3).

I have tried to present some of the problems we face in trying to differentiate between hemophilia and the various bleeding syndromes associated with a long bleeding time. In our experience, von Willebrand's disease has been just as common as hemophilia, and these two conditions are by far the two most common congenital bleeding diatheses. The relative frequencies reported from different laboratories differ depending largely on the criteria they use to diagnose von Willebrand's disease.

DR. FUDENBERG: Dr. Aggeler, would you mind opening the discussion?

TABLE 3.—*Factors in Differential Diagnosis of von Willebrand's Disease*

	von Willebrand's Disease	*Hemophilia*	*Qualitative Platelet Defects*
Bleeding time	Increased	Normal	Increased
Platelet adhesiveness	Decreased	Normal	Normal or decreased
Factor VIII	0-50% (often 30-50%)	0-30% (often <1%)	Normal
Response to transfusion of Factor VIII	Immediate rise to expected or higher level with further progressive rise for 24-48 hours	Immediate rise to expected level, then exponential fall with half-time of 10-16 hours	
Prothrombin consumption	Usually normal	Usually poor (not corrected by platelet substitutes)	Normal or poor (corrected by platelet substitutes)
Clot retraction	Normal	Normal	Normal or poor
Bleeding time corrected by transfusion of	Fresh plasma or cryoprecipitate		Platelets

DR. AGGELER:* I would just like to make some very minor remarks that might help to clarify some of Dr. Perkins' problem cases. One is that aspirin might have a greater effect on the bleeding time in abnormal cases; although, it does have an effect on the bleeding time in normal people too. In an equivocal situation one might be able to bring out a slightly prolonged bleeding time by giving aspirin and checking it two hours later.

I would like to discuss briefly the work of Dr. Sahud[10] to clarify the relationship between aspirin, a type of thrombasthesia, and von Willebrand's disease. There is a type of thrombasthenia, fairly rare I think, that has entirely normal levels of AHF associated with prolonged bleeding time and decidedly impaired platelet adhesiveness. In these patients platelet aggregation tests can be shown to react quite normally to the higher concentrations of ADP, but the platelets do not adhere to collagen fibers, nor are they aggregated by collagen suspensions. This group of patients is obviously very important to identify, since we would want to treat with platelets and not with cryoprecipitate.

The other area in which confusion arises is in the use of "the pill" or in pregnancy where AHF levels may rise (in a pregnant patient particularly). The patient with a baseline level of AHF of 25 percent may have 50 percent (in the last trimester of pregnancy) and the diagnosis of von Willebrand's disease may be missed. The role of "the pill" in raising AHF is a little less clear. If a patient is in mid-cycle; that is, when she has taken "the pill" for a couple of weeks, one may get some rise in AHF level. At the beginning or end of the cycle the rise is apt to be less prominent.

*Paul M. Aggeler, M.D., Professor of Medicine.

QUESTION: What happened to the patient, particularly with respect to his requirement for surgical operation?

DR. PERKINS: He is still waiting for a final decision. I am hopeful we may find some way to avoid operating. I think we have an almost impossible situation—neck dissection needed in an asthmatic, obese, hemophiliac patient, who might react so violently to transfusion therapy that it alone could kill him. I just don't have any good answers to this. If the issue is forced and we are told, "This man will be dead in another six months if operation is not done," we may have to act. Our plan for the moment is to give him the new Hyland Method 4 concentrate, which is a very highly concentrated Factor VIII. We hope that it may be quite deficient in IgA. The volume required to be transfused is very small. That will at least take care of the transfusion reaction problem, and we hope meantime that he can try to reduce the patient's weight and improve his lungs by stopping smoking.*

DR. SALMON:† Have you considered preparing some cryoprecipitate from a donor who lacks IgA?

DR. PERKINS: Yes, that would be a good suggestion provided we could find such a donor who wouldn't mind being plasmaphoresed. We could collect many units from a single donor this way. I think we can get around this problem. The other one, the risk of operation, is more serious. The procedure on the neck demands that we achieve normal hemostasis, and this means a very large amount of Factor VIII concentrate. I calculated

*The Hyland Method 4 concentrate has been tried, and the patient has had no reaction.

†Sydney E. Salmon, M.D., Assistant Clinical Professor of Medicine.

that he will need approximately 32 to 36 units of cryoprecipitate to raise the Factor VIII level to 60 percent and then half that dose every 12 hours for 10 days. This would be the absolute minimum. That is a lot of antihemophilic factor concentrate.

QUESTION: Do corticosteroids inhibit bleeding in von Willebrand's disease? They do in thrombocytopenia.

DR. PERKINS: The reason that bleeding is helped in thrombocytopenia is rather obscure in itself. There is some question that the blood vessel lining is involved in the basic idiopathic thrombocytopenic purpura process. I know of no evidence that steroids help von Willebrand's disease, and I don't know of any studies.

QUESTION: Does inhibitor to Factor VIII develop when treating hemophiliacs with cryoprecipitate?

DR. PERKINS: This can occur in any hemophiliac treated with commercial concentrate, plasma, or cryoprecipitate. There is always the risk of a factor developing which is presumed to be an antibody, which (if potent) will destroy transfused AHF as fast as it goes in. When such an inhibitor develops, transfusion therapy with AHF in any form is usually useless. Such an inhibitor develops in approximately 5.0 percent of hemophiliacs. If elective operation of any kind is planned for a hemophiliac, *in vitro* tests must be run for a circulating anticoagulant against AHF.

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PARENTS' "GUILT" ABOUT CHRONIC ILLNESS

"Personally, I've never seen any parents who didn't have guilt feelings because of the chronic illness, [deformity,] or invariably fatal illness of their child. We assume that they have them. We don't speak to them of guilt feelings; but we sit down and among other things, we say, 'Well, I want to be sure that you're not thinking that something you did or didn't do contributed to this situation.' Sometimes you can just see them heave a sigh of relief. . . . It is amazing how gratified parents are for this open approach and how obviously relieved they are for the absolution of their presumed sin."

—JAMES G. HUGHES, M.D., Memphis

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